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Methodology Issues in Lipid Pharmacoeconomic Investigations. Reactor Panel and Open Forum

J. Sanford Schwartz, MD*; Alistair McGuire, PhD†; Talat Ashraf, MD‡; and Nicolaas Otten, PharmD§

*Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA; †City University, London, UK; ‡PPD Pharmaco, Cary, NC; §Canadian Coordinating Office for Health Technology Assessment, Ottawa, Ontario, Canada

This paper summarizes the responses of a group of panelists to the topic of methodology issues in the pharmacoeconomics of lipid-lowering therapies, presented earlier by Susan Andrade, Tom Delea, Bruce Kinosian, and Joel Hay. Moderated by Sanford Schwartz, the panel included Alistair McGuire, Talat Ashraf, and Nicolaas Otten. Reactions and comments of meeting participants follow.

Moderator: We will start by asking the panel to share their reactions, thoughts, or comments in the area of methodology issues in lipid pharmacoeconomic studies.

Alistair McGuire: I'll begin with a general trend from the last two papers [Kinosian, Hay, this issue] by asking, "How does one know which model to believe?" Even if models are available on the Internet, how do we know which one to take?

Bruce Kinosian: I think the models should be subjected to the same kinds of tests, assuming the data is available, that usually are required in other predicted models. One has to see how well calibrated they are and how well they discriminate. It is now possible to do this because outcome data are available. However, this data may not be readily available to everyone. Unless you happen to work for the owners of the right outcome data, you are left with a trial that's 20 years old. An earlier suggestion by the Moderator to make the outcome results from studies, such as the West of Scotland Coronary Prevention Study (WOSCOPS) [1], the Scandinavian Simvastatin Survival Study (4S) [2], and the Cholesterol and Recurrent Events (CARE) study [3], available to investigators would be a real advance for the field. The results from these trials could be used to test models and validate them.

Alistair McGuire: An added requirement should be that along with the data, the regression analyses should be reported.

Bruce Kinosian: Not only the regression test and input parameters, but also the functional form used, because very different answers can be obtained depending upon the functional form employed.

Talat Ashraf: Journals do not appear to be equipped to handle the details of regression analysis. When one sends regression equations to the journal, 35 pages are submitted and 25 pages come back, asking that they be put into an appendix. It is also asked that the details be sent only to those interested. So that's one of the basic problems: we do send regression equations, but they come back.

Bruce Kinosian: I would say that showing the results of how well calibrated your model is would be more useful than sending the regression equations. Steve Grover has set a standard dictating that one should show that a model is calibrated. One difficulty with his calibrations, however, is that they are calibrated at the mean. So, individual patient predictions are needed to do the validations.

Joel Hay: To address the question of which model one should chose, you have to consider your preferences. The kind of modeling that Tom Delea presented (frontier analysis) [Delea, this issue], that Bruce Kinosian presented (based on clinical trials) [Kinosian, this issue], and the type of modeling that I presented, are very different. One uses surrogate markers and one uses actual outcomes data from clinical trials. The preferences of the decision-maker and what kind of uncertainty they are willing to accept will dictate what kind of models to use. If knowing the relationship between a surrogate marker and an actual end-point is important, then perhaps frontier analysis should not be

Address correspondence to: Dr. Nicolaas Otten, Canadian Coordinating Office for Health Technology Assessment, 110-955 Green Valley Cr., Ottawa, Ontario, Canada K2C 3V4.

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used; if you accept surrogate markers, then that would imply something else.

Moderator: My guess is that if you take the results of 4S [2], CARE [3], and WOSCOPS [1] and you substituted each one of those results into the other model of the same disease, you would end up with three different results for each trial. The problem then becomes, "How is a decision-maker going to assess the relative cost-effectiveness of one drug versus another or one intervention versus another?" It isn't because the models have different assumptions; it is because they have different functional forms. The models have different inputs that vary more than just the inputs of the trial results themselves, and that makes them hard to use. Perhaps the answer is, as Joel Hay suggested, to require people to put their models in the public domain. People wouldn't be able to own their models anymore, but that is the price of publishing. With simple models, it was relatively easy to read an article in a journal, redraw the decision tree, and, using the given parameter estimates, you could substitute numbers and use the model. But the models we are dealing with here are at a different level of complexity.

Nicolaas Otten: What does the decision-maker want in all this? We have several different models with different results, different assumptions, and it gets very complex to sort through. However, no matter which models we have been looking at here, we know that somewhere in the spectrum of these lipid-lowering therapies, treatments are cost-effective. And that was the desired result. What we don't know is where to start and where to stop, and that's where more data collection and more validation of the models come in. We then have to add the real-world situations. From Susan Andrade's study [Andrade, this issue], reviewing utilization patterns shows that how people are or are not taking their prescribed medication varies substantially. In Canada, besides the study Susan mentioned from Saskatchewan, there is also one from Quebec that has very different results. In Saskatchewan, looking at all lipid-lowering agents at the end of 1 year, only 25% were taking their lipid-lowering agents. The average length of time on therapy was 3.7 months. So, economic evaluations out to 5 years and then models to 15 years don't really matter if people are not taking their medication. It is fine to model, but we have to start some up-front work, not only with patient compliance but also with the prescribing habits of physicians. Utilization patterns and prescribing patterns of physicians bear little resemblance to the results in the literature. I think that modeling tells us what the potential is, but there is much work to do in terms of actually seeing the kind of benefits that we are predicting with these models.

Talat Ashraf: We have done some relationship studies and found they are not linear, so I don't accept the idea of models based on percentage changes. The fundamental flaw with the percentage change model is that it is assumed that a 1% reduction in LDL has the same quality for all treatments, but in real life it doesn't have the same quality. Niacin treatment is different from treatment with statins, so you cannot really do percentage change models. On the other hand, models based on clinical trials [Hay, this issue] have more flexibility in this regard.

There are a lot of questions being asked from a managed care perspective these days that are not being answered. Why? Those in managed care want definitive answers to how individual drugs apply to their own plans, and realistically, we do not always respond to these questions with absolute answers. It is asked that models be customized to mimic what happens with a particular drug in their plan. We can perhaps do this with models based on coefficients, customizing the model to a particular managed care situation.

A second issue is that those in managed care want evidence in their setting for the outcomes attributed to a drug. If 10 fewer myocardial infarctions (MIs) are expected by 5 years, some imply, "Let's wait 5 years and see if, in fact, 10 fewer MIs did happen in my plan." How can we address this?

The third story involves the response of managed care to evidence from the literature supporting the use of statins to avert MIs. If one says that, as soon as a patient has an MI, statin should be prescribed, managed care asks, "Why?" All trials prescribed pravastatin 3 months after an MI, so managed care feels that prescribing pravastatin immediately after having an MI is unnecessary. How can we answer that?

To give another example, we went to a physician group and asked why pravastatin or simvastatin or lovastatin were not being prescribed to patients who had experienced an MI. The community physician answered that while the patient was in the hospital, the hospital physicians did not think it was necessary to prescribe statin. If all the tests that had been done in the hospital indicated no statin treatment, then the community physician

offered no treatment. The real-life issue is that if a patient who was prescribed a statin as primary prevention for 2 years has an MI on statin and goes to the hospital, should you keep on prescribing a statin when the patient comes out of the hospital? These are the kind of issues community physicians are asking. These are the type of questions managed care gatekeepers are asking. While I don't think there is a clear answer, I also feel that we may not have presented things clearly to the physicians who would be prescribing these drugs on a daily basis. We are looking at numbers of cost per year of life saved, and that's good for decision analysis, but it won't get the drugs prescribed to patients.

The final issue I want to mention has to do with compliance. The value of 60% discontinuation after the first year comes from somewhere, but managed care won't accept that those prescribed statin will only stay on the drug for 5.8 months; they see the patient as staying in their plan for 2 years and consider 100% compliance to be unnecessary.

Moderator: Susan [Andrade], do you have any responses to the compliance issues that were raised? Did you look at physician prescribing at all?

Alistair McGuire: Could I add in something here on compliance? Did you look at the characteristics of noncompliance at all? Because the figures are so different from one study to another, did they have similar characteristics?

Susan Andrade: In our study, factors associated with discontinuations were looked at. It was found that patient gender and previous discontinuation of therapy were the biggest predictors, but this was not found in other studies such as the Australian study or the Saskatchewan study [Andrade, this issue].

Moderator: In the paper delivered earlier, it was mentioned that in Australia the compliance rates were much lower because the people didn't believe that lipid-lowering therapy was going to do anything for them. I was wondering about the role of public education in trying to improve compliance as opposed to doctors talking to patients.

Susan Andrade: I think both are necessary. First, if we cannot convince the physicians that a treatment is important, we are not going to get the patients to believe it is important. The patients' main support system should be the clinicians who work together with them to treat their condition. Evidently, the system is not presently optimal.

Joel Hay: To comment on the issue of compliance, it is interesting that if a straight naïve economic analysis of compliance is done with the assumption that the effectiveness of the lipid therapy is linearly related to the amount of compliance, one can actually show that it's more cost-effective if patients are not compliant along certain levels. And it may turn out to be true, that taking therapy every other day, or only taking enough therapy to get to 20% LDL reduction using some type of noncompliance, may actually be a much more cost-effective strategy. Only more research will answer this. These types of models can be used to assist in making decisions today about real-world therapy, with the fundamental advantage of models—done properly and laid out clearly—being that one can question them, challenge them, or change them as needed. To be useful, models must be presented in a logical and consistent way with assumptions and parameters of analysis laid out in a completely transparent fashion.

Nicolaas Otten: How much of an impact did non-healthcare costs like those due to employee productivity over the 5 years have in the model you presented [Hay, this issue]? Also, how was this calculated for various ages, such as older age groups versus younger people, or for men or women not in the workforce?

Joel Hay: The employee productivity analysis that was done took data from the National Health Interview Survey for the United States. In the main part of the study, analysis was only done for males aged 45–64 for comparison with the West of Scotland [1] treatment group. The female lifetime projections that were done included cost per year of life saved, but not any employee productivity. In this cohort (males aged 45–64) one doesn't have to worry about the retirement factor. This group has extremely high labor force participation, about 75%. We multiplied workforce participation by average employee compensation based on Bureau of Labor statistics data. We used the National Health Interview Survey to look at both the increased number of sick days reported by patients with ischemic heart disease over and above sick days reported by people that did not have ischemic heart disease, as well as the dropout from workforce due to condition.

Moderator: If older people, say 65, 70, or 75 years of age, were included in the analysis, what would you have done?

Joel Hay: To adjust for employee productivity in a retirement age population where there is less employee productivity than in a nonretirement age population, I think the willingness to pay argument should be used. As a society, we are willing to pay to keep people alive beyond the point at which they stop being productive members of the workforce. This population has utility and value; economics is not about just productivity, it's also about utility and benefits.

Alistair McGuire: One issue that has been raised in these discussions is whether or not we should do economics alongside trials, which partly underlies this idea of modeling and partly underlies the efficacy versus effectiveness idea. There is a whole school of thought that says that trials are not representative of the heterogeneity of a population that you are aiming to treat. Clinical trials tend to screen out patients with comorbidities. Perhaps the argument then becomes a trade-off as to whether or not modeling should be done solely on effectiveness with costs added in with the assumptions at the outset versus using the trial results at all. This argument saddens me because there is a lot of empirical evidence that lipid-lowering therapies work, and people aren't changing their practices. Where are the incentives within the system to get people to, first of all, change their clinical practice given the evidence, and, secondly, change the budget allocations given that it's going to be costly to have effective treatment introduced?

Talat Ashraf: I personally think that every physician believes that decreases in LDL or reduction of LDL/HDL ratios do have clinical benefits. Treating a patient with high cholesterol to reduce heart disease is a reasonable argument, but why is it not practiced? It is a community-based logistical issue that takes into consideration patient behavior and responsiveness; so, while every physician knows that this is a very good thing to do, it is not always practiced.

Bruce Kinosian: It seems that revascularization procedures are used much more than lipid-lowering drugs. Apart from the economic incentive to do procedures, if one goes to managed care plans where your interventionists are salaried and they don't get more money for doing procedures, you still have a lot more procedures done. To use an analogy, there seems to be much more attention to the plumbing than there is to the respective modification of the clogged pipes. If one looks at the revascularization studies, lipid-lowering drugs are a lot cheaper and a lot more effective at preventing MIs than revascularization. Yet, I'm sure that if you surveyed physicians, that is not the answer you would get. Perhaps part of it has to do with education.

Nicolaas Otten: Changing one's behavior, whether a patient's or a physician's, is a very difficult thing. It's not that people don't believe that the changes are good. But altering people's habits is difficult. It has been shown that a 30% change in terms of hard outcomes would result in a change in behavior. There has to be feedback, an interactive situation, to show patients and physicians the impact of what they are doing.

Moderator: This is a question for Bruce Kinosian. You showed a slide indicating that in 4S almost twice the benefit was obtained from getting somebody in the treatment group down to a certain LDL level compared to if that person was at the same level in the placebo group. Is this analogous to what Jim Shepherd went through this morning on the West of Scotland study, which showed that in groups with overlapping levels, people in the treatment group get greater benefit?

Bruce Kinosian: No, it's not analogous. In the overlap group model, the level of LDL cholesterol determines one's destiny, and there is a difference in moving from a higher level to a lower level. Perhaps this has to do with what Dan Rader talked about earlier at this conference in terms of plaque stabilization: reaching a lower LDL level in the treatment group rather than if one was always at that level.

Now, in the analysis of the 4S data, one can estimate the risk equation from the placebo group, substitute the lipid levels of the treatment group, and then look at the actual treatment results from a coefficient on treatment assignment. In this case, one sees about 90% more CHD events averted in the treatment group than would be predicted purely from the observed lipid changes.

Moderator: To what can that be attributed?

Bruce Kinosian: It probably has to do with a few different things, including plaque stabilization and perhaps some factors related to statins in general. This "greater than maximum" benefit can be seen with two different kinds of statins and also with cholestyramine. So, people with plaques at a certain level of risk get more benefits from treatment than what you'd predict for people who always were at that lower level.

Mark Hlatky: Earlier today, Dr. Schwartz mentioned the ways that preventive measures have been adopted in the United States. Sometimes these were adopted by individuals, and their lifestyle changed. Sometimes health plans or insurers paid for treatment, and other times a societal decision was made that something was good, which encouraged other people to implement it. One example is immunization for children. I firmly believe in them, but the typical managed care plan that provides these immunizations doesn't gain from them because these children, particularly in Medicaid programs, have a turnover of over 50% per year. So the original managed care provider is not there when the benefits occur from immunization. Secondly, when there is a long time horizon associated with benefits of a therapy, it will have to be proven that this is beneficial to society using various other intermediate measures. It also won't be easy to sell to a managed care plan because, if they were the only providers of the treatment, everybody at high risk for the disorder would join that plan and they would be overwhelmed. They won't gain any benefit from it in the short run, so perhaps a certain societal rigor will have to be imposed. When it becomes required, then managed care plans will look into the most cost-effective way of providing this necessary service or these necessary prescriptions. Lastly, it would be very interesting to see how many people would use a medication if they had to pay for it entirely by themselves. Even if it is their lives that would be saved or enhanced, I don't think you'd sell very much of that medication. To summarize, it is a question of cost incidence, not just cost and effectiveness.

Talat Ashraf: Perhaps immunization is not a good example. Getting back to lipid-lowering therapies, it is unlikely that any managed care organization would tell their physicians not to treat a patient with hyperlipidemia. Managed care may not have a policy on it, but every managed care organization I know has an antihyperlipidemic agent on the formulary. So the issue really isn't that managed care is not convinced of the therapies: they do have statins on the formulary. Rather, it is the physicians and the patients who are not convinced. It's a benign disease. If one has hyperlipidemia, nothing happens immediately, daily activities go on until one may have a myocardial infarction. Even then, patients who have myocardial infarctions don't take this therapy post-MI. So, with immunization, the cost is for about two shots per child in the plan, whereas with lipid-lowering therapy, the cost of medication is for about 20 years. So it's a different kind of scenario in terms of cost: one is a few million dollars in the plans, of which a part may be paid by the state, versus a multimillion-dollar cost. These two cases are really not comparable.

Moderator: We get impatient when we know there is a treatment of value we can offer and even more impatient in how long it takes to change behavior. We can perhaps learn from other chronic diseases like diabetes and hypertension about changing behavior effectively, or ineffectively.

Speaker 1: It is difficult to be both advocate and analyst in many situations; we worry about persuading people that our model is accurate and valid. Perhaps those of us who see ourselves primarily as analysts, economists, epidemiologists, and such would be better served if we worried less about providing people with the answer ourselves, meaning a simple point estimate of cost-effectiveness and whether it is above or below some appropriate threshold. Rather, providing good information to persons in positions that can make use of the information should be a priority. Tom Delea's presentation [Delea, this issue] of efficiency frontiers was very important in this respect. In fact, he may have undersold that approach by limiting it to surrogate markers. Bruce Kinosian [Kinosian, this issue] applied the same frontier approach to a life-years-saved measure of effectiveness. The point is, instead of trying to summarize all this information in a simple ratio that is very limited, the audience is given more complete information with assumptions clearly explained. Joel Hay's suggestion [Hay, this issue] that there is nothing wrong with models provided that they are clearly and transparently presented to the audience is key.

Moderator: The importance of the model is not necessarily a point estimate, but understanding what is driving the model and under what conditions the model might hold. When a model is presented and a result of cost per year of life saved is given, it can be put into one of three categories. Is it clearly cost-effective? Is it clearly not cost-effective? Or is this going to be a judgment call? There are so many variations that go into how a model is created. My feeling is you can't take published models from peer-reviewed journals and compare one number to another number because the models are so different.

Speaker 2: The lipid field is an area where we really do have a lot of outcomes data; there are

about 150,000 patient years of rigorous follow-up in randomized controlled clinical trials. It is ironic that treatment to goal in diabetes and hypertension, where there is less rigorous data on specific products and specific therapeutic interventions, is accepted; however, for lipid-lowering agents, treatment patterns are much less aggressive.

Moderator: In hypertension, the issue really is about prevention, and physicians in the United States are not very oriented toward prevention. The medical profession is being coerced in that direction, but it is going to take a long time to achieve.

Bruce Kinosian: The major difference between diabetes goals and lipid goals has to do with the more immediate consequences of not treating diabetes to goal. However, very few people think they suffer any sequelae from hyperlipidemia, so clearly, time horizons vary between the two.

Moderator: To close, in this session we have clearly identified some of the real-world problems and limitations of treating patients with lipid-lowering therapies. However, the management of hyperlipidemia, as well as the attitudes and the knowledge of how to manage it, have been advanced not only by the clinical trials but also by the economic analysis of lipid-lowering agents that have been presented.

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